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(54) Electrophoresis apparatus.

(57) In known electrophoresis apparatus, the directional modulation of the electric field used in electrophoresis is limited by the configuration of the electrode arrays. In the present invention, greater flexibility in directional modulation of an electric field is provided. Apparatus according to the invention comprises a support (20, 22, 24, 26, 28) in which a medium for electrophoresis is placed, the medium being in the form of a gel (G) and a liquid buffer. A plurality of driving electrodes (D_n) are arrayed in spaced relation to one another so as to contact the medium. A plurality of sensing electrodes (S_n) are also arrayed so as to contact the medium and are spaced relative to one another and to the driving electrodes. Each sensing electrode is preferably positioned radially inward of and paired with a single one of the driving electrodes. Electrical potentials are applied to selected ones of the driving electrodes (D_n) and means are provided for sensing electrical potentials at selected ones of the sensing electrodes (S_n) and for adjusting the applied potentials to maintain the sensed potential at a selected value at a sensing electrode of each pair. The apparatus may be programmably controllable so as to enable an electric field to be modulated in both amplitude and direction as a function of time.

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ELECTROPHORESIS APPARATUS

This invention pertains to electrophoresis. More specifically, this invention pertains to improvements in electrophoresis apparatus whereby an electric field can be directionally modulated, so as to tend to cause a molecule being electrophoresed to migrate in any desired direction.

It has been known heretofore that electrical parameters governing gel electrophoresis, i.e., electrophoresis on a flat surface of a gel, in a buffer solution, include the intensity of the electric field, the direction of the electric field, and the evolution of the intensity and direction of the electric field as functions of time, as well as the type and temperature of the buffer solution, the material and configuration of the electrodes, and other factors. Both homogeneous and nonhomogeneous electric fields have been used in gel electrophoresis. An electric field is regarded as homogeneous if it is uniform, in intensity and direction, across the flat surface of the gel at any moment in time.

It also has been known heretofore that pulsed modulation of the intensity of the electric field, its direction, or both, enhances the utility of gel electrophoresis, particularly in the separation of proteins, nucleic acids, and other such macromolecules. Pulsed modulation refers to modulation at timed intervals, between which the electric field may be substantially uniform across the flat surface of the gel.

In recent years, apparatus for gel electrophoresis have advanced from apparatus employing two parallel driving electrodes, or two parallel arrays of driving electrodes, which apply electric fields tending to cause molecules to migrate along straight lines between such electrodes, to apparatus employing polygonal arrays of driving electrodes, which apply electric fields that can be directionally modulated so as to tend to cause molecules to migrate along non-straight paths, e.g., paths having corners or zig-zag paths.

In one heretofore known type of apparatus for gel electrophoresis, as mentioned above, a square array of driving electrodes is provided, which enables electric fields to be alternatively applied in transverse directions so as to tend to cause samples being electrophoresed to migrate in paths that change direction at 90° angles. See, e.g., Cantor et al, U.S. Patent No. 4,473,452, which discloses that such fields can be substantially uniform, if applied by and between paired electrodes in like numbers on opposite sides of the square array, or substantially fan-shaped, if applied by and between one electrode on one end of a given side of the square array and a plurality of electrodes on the opposite side of the square array. This patent also mentions that each electrode can be selectively maintained at any positive or negative electrical potential within a selected range.

In another heretofore known type of apparatus for gel electrophoresis, as mentioned above, a hexagonal array of driving electrodes is provided, which enables homogenous electrical fields to be alternatingly applied at timed intervals so as to cause molecules being electrophoreses to migrate in zig-zag paths. See, e.g., Biotechnology, December 1986, page 1054, which refers to electrophoresis in such apparatus as contour-clamped homogeneous electric field (CHEF) electrophoresis, and which compares CHEF electrophoresis to other heretofore known techniques including pulsed-field gel electrophoresis (PFGE) and field-inversion electrophoresis. See, also, Chu et al., "Separation of Large DNA Molecules by Contour-Clamped Homogenous Electric Fields," Science, December 19, 1986, Vol. 234, pp. 1582-5. An apparatus employing parallel driving electrodes, for field-inversion electrophoresis, is disclosed in Carle et al, U.S. Patent No. 4,737,251.

Although some of the heretofore known apparatus and techniques discussed in the preceding paragraphs have been valuable contributions to the art of electrophoresis, a problem addressed by the invention is the need for greater flexibility in directional modulation of an electric field in an apparatus for electrophoresis.

In accordance with the present invention, apparatus for electrophoresis is provided which comprises a support containing a medium including a buffer solution; a plurality of driving electrodes in contact with the medium and arrayed in spaced relation to one another; and supply means for supplying electrical potentials to the driving electrodes, characterized in that the apparatus further includes a plurality of sensing electrodes in contact with the medium and arrayed in spaced relation to one another and to the driving electrodes; sensing means for sensing electrical potentials at the sensing electrodes, and adjusting means for adjusting the potentials applied to the driving electrodes to maintain the potentials sensed by the sensing electrodes at selected values.

It is an advantageous feature of the invention that each driving electrode may be independently controlled and the apparatus may be programmably controllable, as for example by means of a microprocessor, to enable an electric field to be directionally modulated, in any direction, e.g., as a function of time.

The present invention will now be described by way of example with reference to the accompanying drawings in which:

FIGURE 1 is a semi-diagrammatic view, partially in section, of a support for an electrophoresis gel, a circular array of driving electrodes, a circular array of sensing electrodes, and an exemplary portion of electrical circuitry associated with the driving and sensing electrodes, in an electrophoresis apparatus constituting a preferred embodiment of this invention;

FIGURE 2 is a block diagram of other portions of electrical circuitry of the electrophoresis apparatus of FIGURE 1; and

FIGURE 3 is a plot of isopotential contours achieved using the apparatus of this invention.

As represented in the drawing, an apparatus for electrophoresis employing a gel matrix G, in a buffer solution, constitutes a preferred embodiment of this invention.

Such a gel matrix and such a buffer solution are conventional in gel electrophoresis. In the preferred embodiment, the gel matrix G may be an aqueous gel of 1% agarose occupying a square area, which measures about 20cm x 20cm. Any conventional buffer solution compatible with the gel matrix G may be used. The buffer solution must have sufficient resistivity to avoid short-circuits between driving electrodes described below. Two preferred formulations for buffer solutions are set forth below in Tables A and B respectively. Preferably these are used in 0.5X strengths.

TABLE A

TAE	(IX formulation)
0.04 0.001	Molar Tris-acetate [Tris(hydroxymethyl)aminomethane acetate] Molar EDTA [ethylenediamenetetraacetic acid]
balance, water pH = 8.0 approximately	

TABLE B

TAE	(10X formulation)
0.89 0.89 0.02	Molar Tris Base [Tris(hydroxymethyl)aminomethane] Molar Boric Acid [H_3BO_3] Molar EDTA [ethylenediamenetetraacetic acid]
balance, water pH = 8.3 approximately	

The apparatus 10 comprises an electrophoresis chamber of a conventional type including a rectangular, horizontal support 20 for the gel matrix G and the buffer solution and including outer walls 22, 24, 26, 28, which contain the buffer solution. The horizontal support 20 and the outer walls are made of a non-electrically conducting material, e.g., glass or plexiglass.

In order to maintain the homogeneity of the electric field, the depth and temperature uniformity of the buffer solution should be controlled, and the gel matrix G should be immersed entirely within a uniform layer of the buffer solution, not recessed into a well. For example, it is believed that a 1% depth variation leads to a localized 1% error in the intensity of the electric field; the direction of the electric field is also affected, but in a more complex way, which is believed to depend upon the depth variation gradients. The buffer solution should be cooled, in order to maintain a uniform temperature, by recirculating through cooling means (not shown) conventional in electrophoresis. Precise temperature control is important because the conductivity of a buffer solution can vary by as much as 3% per degree C variation.

Preferably, the support 20 is levelled, and the buffer solution covers the gel matrix G at a depth of about 1cm and is maintained at a uniform temperature between 5 and 15° C. Maintaining the buffer solution at such a temperature also suppresses denaturing of the gel matrix G and of the sample.

The apparatus 10 comprises twenty-four driving electrodes D_n (wherein n represents integers from 1 to 24 inclusive) in a circular array having a radius R_D and twenty-four sensing electrodes S_n (wherein n again represents integers from 1 to 24 inclusive) in a circular array having a radius R_s and being disposed fixedly

and concentrically within the circular array of driving electrodes. The circular arrays of the driving electrodes D_n and sensing electrodes S_n preferably form closed paths, and in the described embodiment these closed paths are closed circles. Each of the driving and sensing electrodes is preferably mounted to make optimal electrical contact with the liquid buffer in the electrophoresis chamber of the apparatus 10, by penetrating the buffer solution vertically over its full depth. Each of the driving electrodes may be advantageously made of a platinum foil covering a cylindrical core, or of coiled or folded lengths of platinum wire longer than the depth of the buffer solution, or of a porous conductive ceramic, e.g., a porous titanium suboxide available commercially from Ebonex Technologies, Inc. under the "Ebonex" trademark. Each of the sensing electrodes may be advantageously made of a platinum wire or other conducting media. In the preferred embodiment, the circular array of the sensing electrodes has a radius R_s of about 16.5cm, the circular array of driving electrodes has a radius R_D of about 18cm, and the geometric center of the 20cm x 20cm square occupied by the gel matrix G coincides with the common center of the circular arrays. A reference radius R_R is indicated on FIGURE 1 for a purpose to be later mentioned. The driving electrodes are arrayed in equally spaced relation to one another, i.e., at 15° intervals. The sensing electrodes are arrayed similarly, at like intervals, so that each of the sensing electrodes is positioned radially inward of one of the driving electrodes. Thus, the driving electrode D_1 and the sensing electrode S_1 are located on a common radius, i.e., the reference radius R_R the driving electrode D_2 and the sensing electrode S_2 are located on a common radius, and so on. The driving and sensing electrodes are arrayed, on the common radii, in electrode pairs. Thus, the driving electrode D_1 and the sensing electrode S_1 constitute a first electrode pair, the driving electrode D_2 and the sensing electrode S_2 constitute a second electrode pair, and so on.

Since the electrophoresis chamber of the apparatus 10 contains a bounded, uniformly electrically conducting layer of the buffer solution, the potential distribution necessary for a homogeneous field within the boundary of such layer is the same as would exist if such layer were embedded in a much larger region exhibiting a homogeneous field. Field conditions within a region isolated as if removed from a larger whole can be maintained if boundary conditions of the region can be matched. The apparatus 10 enables the boundary conditions of the circular array of sensing electrodes to be matched as if the circular array of sensing electrodes were within a much larger region exhibiting a uniform field.

At each electrode pair constituted by a driving electrode and a sensing electrode, an electrical potential is applied directly to the driving electrode, e.g., between the driving electrode and a point of common potential usually referred to as ground, of a suitable magnitude to cause an electrical potential of a desired magnitude to occur at the sensing electrode of such electrode pair. Moreover, the electrical potential is sensed at the sensing electrode of such pair. The potential required at each sensing electrode varies depending on the desired field. In turn, the potential at the corresponding driving electrode differs from that of its sensing electrode by varying amounts, as determined by parameters such as buffer solution formulation, electrical current, electrode polarity, and spacing.

To establish a uniform field of a desired intensity $\underline{E}$, e.g., between $2Vcm^{-1}$ and $10Vcm^{-1}$, in a desired direction from the center of the circular arrays, as shown by an arrow representing a vector in FIGURE 1, the required potential or voltage at any given one of the sensing electrodes is given by the equation:

$$V_s = \underline{E}R_s\cos\theta$$

where $\underline{E}$ is the desired electric field intensity, as mentioned above,
R_S is the radius of the circular array of sensing electrodes, and θ is the angle between a radius through the given one of the sensing electrodes and a radius coinciding with the vector arrow, as shown in FIGURE 1. The electrical potential at a central region C of the gel matrix G may be arbitrarily held at zero potential, and, therefore, the central region C of the gel matrix G may be said to be grounded. Typically, for an electric field having an intensity between $2Vcm^{-1}$ and $10Vcm^{-1}$, potentials or voltages of up to ± 165V are sensed at the sensing electrodes. Typically, the electrical potentials applied at the driving electrodes are up to 25V greater, more commonly up to 15V greater, than the electrical potentials sensed at the sensing electrodes. Since the direction of the electric field can be quite arbitrary, it is not necessary to align the direction of the electric field with the angular position of any electrode or electrode pair of the circular arrays.

As a representative example, for an electric field having an intensity of $5Vcm^{-1}$ and being directed at an angle of 25° clockwise (as shown) from the reference radius R_R, the required potentials or voltages at the sensing electrodes are given below in Table C, wherein the number in the column at the extreme left is the subscript of the designation of the sensing electrode, and wherein all data are approximate.

TABLE C

Electrode	θ^*	$\cos\theta$	$Vs(= E R_s\cos\theta)$
1	335°	0.906	74.7V
2	350°	0.985	81.3V
3	5°	0.996	82.2V
4	20°	0.940	77.5V
5	35°	0.819	67.6V
6	50°	0.643	53.0V
7	65°	0.423	34.9V
8	80°	0.174	14.3V
9	95°	-0.087	-7.2V
10	110°	-0.342	-28.2V
11	125°	-0.574	-47.3V
12	140°	-0.766	-63.2V
13	155°	-0.906	-74.8V
14	170°	-0.985	-82.2V
15	185°	-0.996	-82.2V
16	200°	-0.940	-77.5V
17	215°	-0.819	-67.6V
18	230°	-0.643	-53.0V
19	245°	-0.423	-34.9V
20	260°	-0.714	-14.3V
21	275°	0.087	7.2V
22	290°	0.342	28.2V
23	305°	0.574	47.3V
24	320°	0.766	63.2V

* Measurements are made clockwise from vector $\underline{E}$.

A constant positive or negative potential or voltage may be arbitrarily added to all potentials or voltages given in Table C above. The corresponding absolute values of the electrical potentials applied to the driving electrodes exceed the absolute values of the electrical potentials sensed at the sensing electrodes in the respective electrode pairs, typically by up to 25V, more commonly up to 15V, but depend in complex ways on such factors as the composition of the buffer solution, the polarities, currents drawn by the respective electrodes, and surface areas of the respective electrodes.

Advantageously, the feedback approach taken by this invention allows such factors as are mentioned in the preceding paragraph to be largely ignored. Prudence still dictates, however, that driving electrodes having larger surface areas are preferred over thin wires. Larger surface areas diminish the potential drops in the immediate vicinity of the driving electrodes and lessen the density of gas bubbles formed by electrolysis, thus reducing excess power dissipation outside the electrophoresis region. Reduced power loss minimizes the cooling requirements. For example, driving electrodes with an exposed surface area of about $0.25cm^2$ are preferred.

Herein, all references to a driving electrode are intended to refer to an electrode which, at a given potential applied thereto, provides or receives an electromotive force tending to cause molecules to migrate toward or away from an electrode of a different potential, e.g., zero potential or a potential of an opposite polarity. For example, if it were grounded, the center C of the gel matrix $\underline{G}$ would define a ground potential of zero value vis-a-vis each of the driving electrodes to which electrical potentials are applied. Irrespective of whether the center C of the gel matrix $\underline{G}$ is at ground potential, electrical potentials can be thus applied to a selected two or more, and as many as all of the driving electrodes, to establish an electric field in an arbitrary direction. Therefore, herein, all references to selected ones of the driving electrodes are intended to refer to as few as two of the driving electrodes, and to as many as all of the driving electrodes. Similarly, herein, all references to selected ones of the sensing electrodes are intended to refer to as few as two of the sensing electrodes and as many as all of the sensing electrodes.

A high gain, error-sensing, differential amplifier arranged for negative feedback is provided for each of

the twenty-four electrodes pairs. As representative examples shown in FIGURE 1, such an amplifier 40 is shown, as provided for the electrode pair constituted by the driving electrode D_{23} and the sensing electrode S_{23}, and another such amplifier 40′ is shown, as provided for the electrode pair constituted by the driving electrode D_{19} and the sensing electrode S_{19}. Each amplifier comprises a high gain, integrated circuit operational amplifier with a discrete component output stage employing conventional high voltage MOS transistors, to deliver output voltages of up to ± 250V, and capable of switching speeds on the order of 100μs. The output stage of each amplifier is connected directly to the driving electrode of the electrode pair for which such amplifier is provided. As a representative example shown in FIGURE 1, the output stage of the amplifier 40 is connected directly to the driving electrode D_{23}.

Each amplifier compares an electrical potential corresponding to the electrical potential sensed at the sensing electrode of the electrode pair for which such amplifier is provided, to a program voltage supplied to such amplifier for such electrode pair in a manner to be later described. The electrical potential sensed at the sensing electrode of such electrode pair may be and, as shown, is scaled down by a factor of 100, before being fed back to such amplifier, by a voltage divider comprising a resistor connected to the sensing electrode of such electrode pair and a resistor connected between the resistor and ground. As a representative example shown in Figure 1, a voltage divider scaling down the electrical potential sensed at the sensing electrode S_{23} comprises a resistor 42 having a resistance of 1MΩ connected to the sensing electrode S_{23} and a resistor 44 having a resistance of 10kΩ connected between the resistor 42 and ground. Such resistor values produce negligible current flow through the sensing electrodes and allow them to sense the buffer solution potential at their locations without errors due to electrochemical electrode activity. Similarly, as shown, a voltage divider scaling down the electrical potential sensed at the sensing electrode S_{19} comprises a resistor 42′ connected to the sensing electrode S_{19} and a resistor 44′. Each amplifier applies an electrical potential having a value equal to a program voltage plus or minus a feedback voltage to the driving electrode of the electrode pair for which such amplifier is provided. The feedback voltage is determined by the electrical potential or voltage sensed at the associated sensing electrode of the electrode pair, and scaled down by the associated voltage divider so as to be in the same range of magnitude as the program voltage. Consequently, an electrical potential of the desired magnitude tends to occur at the sensing electrode of such electrode pair.

As shown in FIGURE 2, the program voltage for each electrode pair is provided, as a digital signal, from a data source 50, which generates or retrieves such program voltage. Further, the data source 50 supplies the digital signal through a digital-to-analog converter 52, which converts the digital signal to an analog voltage, through a buffer 54, which buffers the analog voltage, and through a multiplexer 60, to the amplifier provided for such electrode pair. The multiplexer 60, which has a timed cycle that may be controlled by the data source 50 through a lead 62, or independently, has one input stage, which is connected to the digital-to-analog converter 52 through the buffer 54, and twenty-four output stages, one for each electrode pair. The output stage of the multiplexer 60 for each electrode pair includes an output terminal, which is connected to the amplifier for such electrode pair, and a capacitor for storing a voltage, i.e., the program voltage supplied by the multiplexer 60 to the amplifier for such electrode pair. Thus, as shown in FIGURE 2, the multiplexer 60 has an output stage including such an output terminal V_1 and such a capacitor C_1 for the electrode pair constituted by the driving electrode D_1 and the sensing electrode S_1 and such an output terminal V_2 and such a capacitor C_2 for the electrode pair constituted by the driving electrode D_2 and the sensing electrode S_2. Also as shown in FIGURE 2, the multiplexer 60 has such an output terminal V_{23} and such a capacitor C_{23} for the electrode pair constituted by the driving electrode D_{23} and the sensing electrode S_{23} and such an output terminal V_{24} and such a capacitor C_{24} for the electrode pair constituted by the driving electrode D_{24} and the sensing electrode S_{24}. The output terminal V_{23} is shown also in FIGURE 1.

In place of the multiplexer 60, a plural number of multiplexers may be used, each addressing a different group of the electrode pairs, e.g., six multiplexers, each addressing a different group of four electrode pairs, whereupon, in place of the digital-to-analog converter 52 and the buffer 54, as a subcombination, a like number of subcombinations of digital-to-analog converters and buffers may be used, each subcombination comprising a digital-to-analog converter supplying an analog signal through a buffer, and each subcombination addressing a different one of the multiplexers. Although shown with a mechanical symbol, the multiplexer 60 preferably is electronic.

The data source 50 may be any suitable source of digital signals representing the program voltages for the driving electrodes. Thus, the data source 50 may comprise a computer, microprocessor, or programmable controller, which generates such signals pursuant to a stored program. The stored program may reside in an erasable, programmable, read-only memory (EPROM) which is used as a "look up" table, and from which data are retrieved, as digital signals, pursuant to external control through external leads 56, 58,

shown in FIGURE 2. External control of such a memory may be provided by an array of switches. In a simpler form, the data source 50 may comprise a resistor-divider string, which is adapted to be selectively switched. Details of the data source 50 are outside the scope of this invention.

The amplifiers noted above and the voltage dividers associated therewith apply electrical potentials, as provided by the digital-to-analog converter 52 through the buffer 54 and the multiplexer 60, to selected ones of the driving electrodes. As the voltage dividers sense electrical potentials at selected ones of the sensing electrodes, the amplifiers adjust the applied potentials so as to tend to maintain the sensed potentials at selected values. The driving electrodes to which electrical potentials are applied and the sensing electrodes at which electrical potentials are sensed are selected from the same electrode pairs. Moreover, the capacitors noted above store the program voltages, and the multiplexer restores the program voltages periodically, e.g., every 200 to 600μs, to the potentials stored by such capacitors.

By appropriate selection and timed control of the program voltages to be thus applied to selected ones of the driving electrodes, the apparatus 10 may be readily adapted to practice a wide range of different techniques of gel electrophoresis, as exemplified by but not limited to such techniques as are discussed in the Cantor et al. and Carle et al. patents noted above and in the Biotechnology and Science references noted above.

A uniform field that is constant as a function of time can be thus used to separate smaller molecules of a sample. Forcing the molecules of a sample to change direction of movement at an angle, however, causes the smaller molecules to proceed faster than the larger molecules.

To practice gel electrophoresis according to a technique similar to the technique discussed in the Cantor et al. patent noted above, the electric field discussed in the above example as having an intensity of $5Vcm^{-1}$ and as being directed at an angle of 25° (clockwise as shown) from the reference radius R_R can be initially applied for a specified period of time, e.g., from 1s to 120s, or more, whereupon the electric field can be angularly rotated 90° (i.e., new electrical potentials are applied to the driving electrodes so that the potential or voltage sensed initially at the sensing electrode S_1 is sensed at the sensing electrode S_7, so that the potential or voltage sensed initially at the sensing electrode S_2 is sensed at the sensing electrode S_8, and so on) and then applied for the same period of time, or for a different period of time, whereupon the electric field can be similarly rotated back (to where the electric field was applied initially) and then applied for the same period of time, or for a different period of time, and so on for a desired number of such alternations of the electric field.

To practice gel electrophoresis according to a technique similar to the technique disclosed in the Carle et al. patent noted above, the electric field discussed above as having an intensity of $5Vcm^{-1}$ and as being directed at an angle of 25° (clockwise as shown) from the reference radius R_R can be initially applied for a specified period of time, e.g., about 120s, whereupon the electric field can be angularly rotated 180° (i.e., new electrical potentials are applied so that the potential or voltage sensed initially at the sensing electrode S_1, is sensed at the sensing electrode S_{13}, so that the potential or voltage sensed initially at the sensing voltage S_2 is sensed at the sensing electrode S_{14} and so on) and then applied at a selected, lower intensity, e.g., $5/3Vcm^{-1}$, for the same period of time, or $5Vcm^{-1}$ for a shorter (e.g., 40s) period of time, whereupon the electric field can be similarly rotated back (to where the electric field was applied initially) and then applied at its original intensity of $5Vcm^{-1}$ for the same period of time, and so on for a desired number of such alternations of the electric field.

To practice gel electrophoresis according to a technique similar to the technique discussed in the Biotechnology reference noted above, an electric field can be analogously switched back and forth 120°, at timed intervals.

The electric field also may be so controlled as to undergo many small step changes in intensity and/or direction in a rapid sequence, so as to approximate a smooth evolution of angle and intensity, over time. As will be apparent from the earlier discussion, any angle of electric field can be programmed, and within the ± 250V constraints of amplifier 40, any intensity between 0 and 10 Vcm^{-1} can be programmed. The field can also be controlled to cause a funneling effect tending to narrow a band of molecules of a sample being electrophoresed as the band progresses along the gel matrix G.

FIGURE 3 illustrates the kind of uniform field that can be generated in matrix G, as actually measured as isopotentials using the arrangement of Figure 1. In this experiment, electric vector E was directed towards electrodes D_{22} and S_{22}. The buffer was 1 cm deep (0.5X TBE formulation), at about 28° C, with a voltage gradient of about $5Vcm^{-1}$ and power dissipation in the buffer of about 60W.

Various modifications may be made in the apparatus 10 without departing from the scope and spirit of this invention.

Claims

1. Apparatus for electrophoresis comprising a support (20, 22, 24, 26, 28) containing a medium (G) including a buffer solution; a plurality of driving electrodes (D_n) in contact with the medium (G) and arrayed in spaced relation to one another; and supply means (50, 52, 54, 60) for supplying electrical potentials to the driving electrodes (D_n), characterized in that the apparatus further includes a plurality of sensing electrodes (S_n) in contact with the medium (G) and arrayed in spaced relation to one another and to the driving electrodes (D_n); sensing means (42, 44; 42′, 44′) for sensing electrical potentials at the sensing electrodes (S_n), and adjusting means (40; 40′) for adjusting the potentials applied to the driving electrodes (D_n) to maintain the potentials sensed by the sensing electrodes (S_n) at selected values.

2. Apparatus according to claim 1 wherein each sensing electrode (S_n) is associated with at least one of the driving electrodes (D_n)

3. Apparatus according to claim 2 wherein each sensing electrode (S_n) is paired with a single one of the driving electrodes (D_n).

4. Apparatus according to claim 1 to 3 wherein the driving electrodes (D_n) and sensing electrodes (S_n) are arrayed along closed paths.

5. Apparatus according to claim 1 to 4 wherein the driving electrodes (D_n) and sensing electrodes (S_n) are arrayed along curved paths.

6. Apparatus according to claim 5 wherein the driving electrodes (D_n) and sensing electrodes (S_n) are arrayed in concentric circles.

7. Apparatus according to claim 6 wherein the driving electrodes (D_n) are arrayed in a circle which is positioned radially outward of a circle in which the sensing electrodes (S_n) are arrayed.

8. Apparatus according to claim 7 wherein each sensing electrode (S_n) is positioned radially inward of and paired with a single one of the driving electrodes (D_n)

9. Apparatus according to claim 8 wherein the sensing electrode (S_n) and driving electrode (D_n) of each electrode pair are located on the same radius.

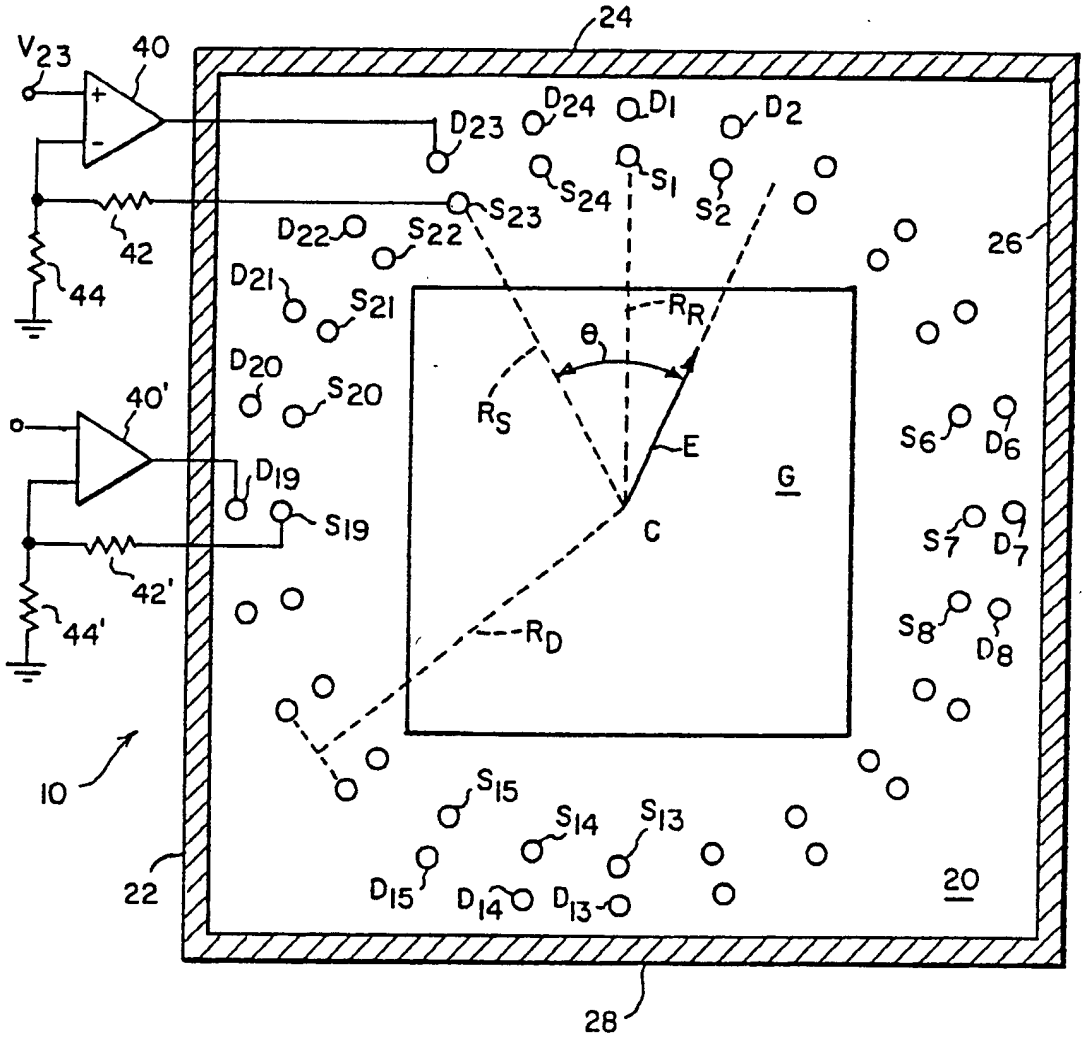
10. Apparatus according to any one of the preceding claims wherein the supply means includes a data source (50) which generates or retrieves a digital program voltage which is converted to an analog signal by a digital-to-analog converter (52) prior to being passed to a multiplexer (60) to apply the electrical potentials to driving electrodes (D_n).

11. Apparatus according to claim 10 wherein the adjusting means (40; 40′) comprises an operational amplifier for each electrode pair and which is positioned to pass signals from the multiplexer (60) to the associated driving electrode (D_n), each amplifier comparing the potential sensed by the associated sensing electrode (S_n) with a value determined by the program voltage to adjust the electrical potential applied to the associated driving electrode (D_n)

12. Apparatus according to any one of the preceding claims further including a plurality of capacitors (C_n) which store the values of electrical potential, and means for restoring the stored potentials periodically to the values of the program voltages, each capacitor (C_n) being associated with one of the driving electrodes (D_n)

13. Apparatus according to any one of the preceding claims wherein the driving electrodes (D_n) have a surface area in contact with the buffer solution of about 0.25 cm^2.

FIG. 1


24
V23
40
D23
D24
D1
D2
S24
S1
S2
S23
D22
S22
42
44
26
D21
S21
RR
θ
D20
S20
40'
RS
E
S6
D6
D19
S19
G
C
S7
D7
42'
44'
RD
S8
D8
10
S15
S14
S13
22
D15
D14
D13
20
28

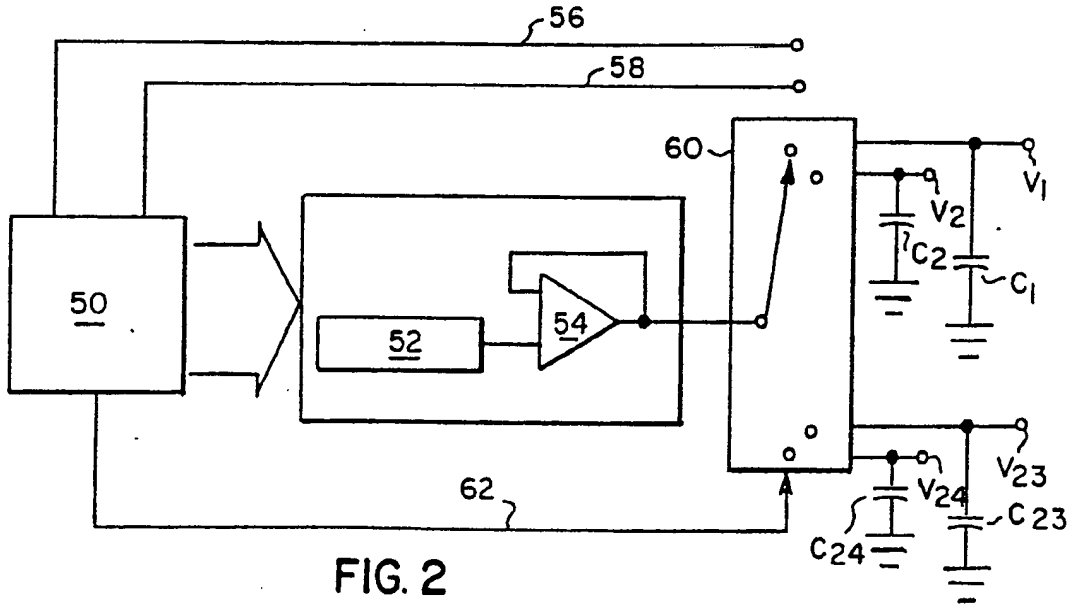

56
58
60
V1
V2
C2
C1
50
52
54
62
V23
V24
C23
C24

FIG. 2

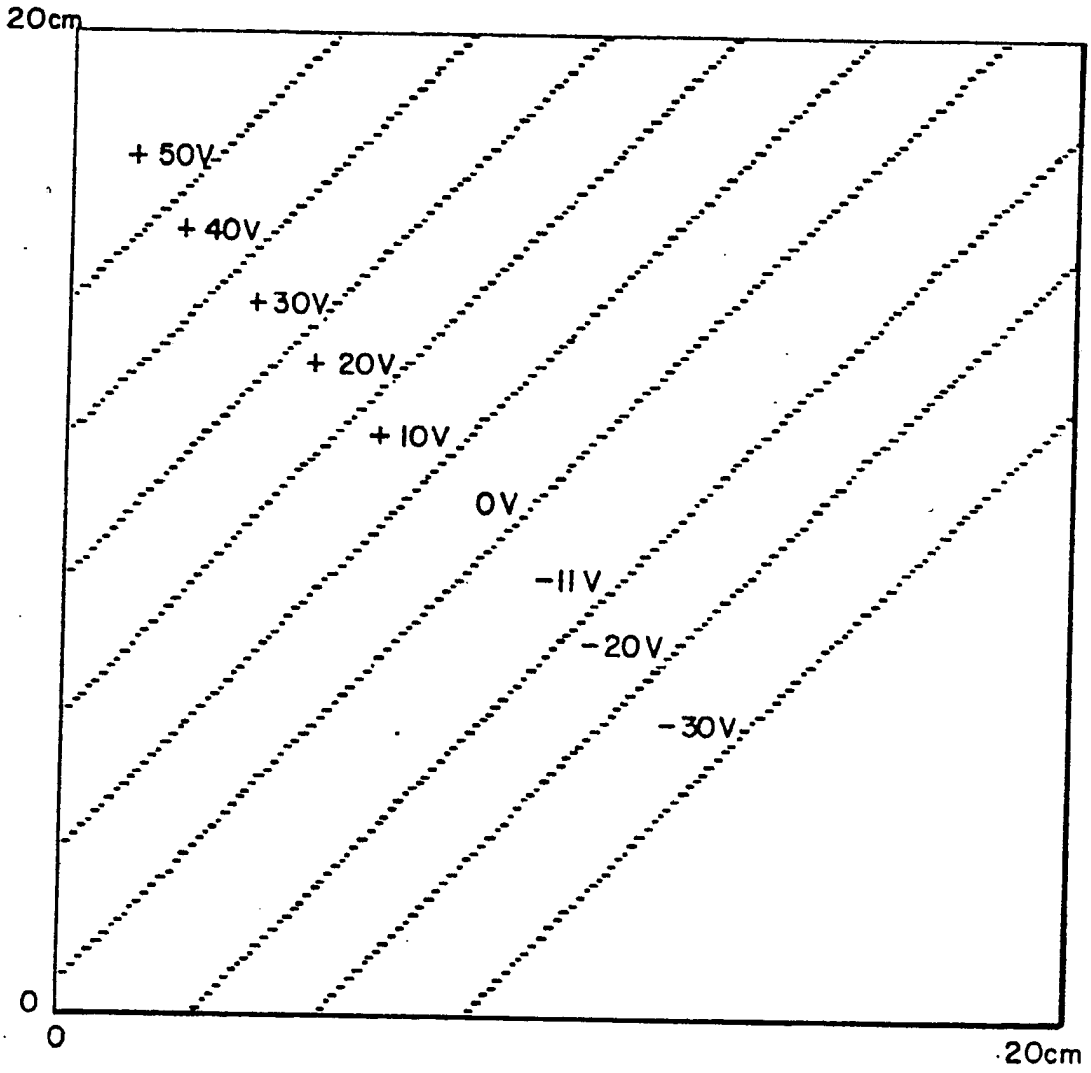


FIG. 3